73. (New) A method of achieving binding between the conjugate of claim 1 and μ opioid receptors comprising administering to the subject in need thereof the conjugate for a time and under conditions effective to achieve binding between said conjugate and μ opioid receptors.

74. (New) A composition comprising a pharmaceutically acceptable carrier and a conjugate according to claim 1 in an amount effective to bind μ opioid receptors.

75. (New) A composition comprising a pharmaceutically acceptable carrier, and a conjugate according to claim 1 in an amount effective to stimulate erythroposiesis.

76. (New) A composition comprising a pharmaceutically acceptable carrier, and a conjuage according to claim 1 in an amount effective to induce retraction of osteoblasts.

77. (New) The peptide conjugate of claim 1, wherein the conjugate is represented by the following sequence: Ac-Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-$(Lys)_6$-NH_2 or a fragment thereof.

REMARKS

As an initial matter, Applicant and the undersigned wish to express thanks to the Examiner for the many helpful comments found throughout the outstanding Office Action.

Applicants also gratefully acknowledge withdrawal of prior rejections under §102. See pg. 2 of the Action.

Claims 1, 19, 26, 32, 52, 54, 57, 64 and 68 have been amended to improve claim clarity.

New claims 73-76 have been added at the suggestion of the Examiner. New claim 77 features a particular peptide conjugate or fragment in which X is alpha-melanocyte stimulating hormone (MSH) and Z is hexalysine.

Support for the claim amendments and new claims can be found throughout the present disclosure including the Drawings and claims as filed originally.

For instance, specific support for new claim 77 can be found at pg. 10, line 3; and pg. 11, lines 25-26. Particular alpha-MSH fragments are disclosed at pg. 11, lines 1-3, for instance.

No new matter has been added by virtue of the claim amendments or new claims.

The undersigned will be contacting the Examiner by telephone to address any outstanding issues not addressed by this submission.

At pg. 2 of the Action, claims 13-18, 21-23, 27, 28, 62, 69, 71 and 72 have been withdrawn from consideration on grounds that the claims do not encompass elected specie. Applicant respectfully requests that the withdrawn claims joined to those now before the Examiner ie., claims 1, 2 6-32, and 52-72. Consideration of the withdrawn claims would not be an undue burden on the Office as it is expected that any search done for these claims would overlap substantially with the search already conducted by the Examiner.

Specifically, withdrawn claims 69 and 72 relate merely to the position of the X and Z group to each other. The claims should be considered in this case because a search for those claims would overlap substantially with the search already conducted by the Examiner. Such action is respectfully requested.

Turning to pg. 4 of the Action, the Examiner requested that "modified fragment" language be removed from claim 68. Applicant has complied with that request by this submission. Claim 68 has been amended.

With respect to the alleged need to submit a substitute specification, the undersigned will comply under separate cover. It is understood from the Action at pg. 4 that the sequence listing

requirement will be maintained so long as claim 68 features fragment language. Claim 68 has been amended in line with the Examiner's request. Indication that the case is in full compliance with the sequence rules would greatly assist the undersigned.

In this regard, it is respectfully noted that none of the text referred to on pg. 3 of the Action ie., "enkephalin, Leu-enkephalin, ..." is an amino acid sequence as that term is defined in 37 CFR §1.821(a). That is, the text is not " an unbranched sequence of four or more amino acids". §1.821(a). Accordingly, the text at issue should not be subjected to a sequence listing requirement pursuant to §1.821(a).

Moreover, since the text at issue refers to amino acid information known in the field as of the priority date of this case, it should not be subjected to a sequence listing requirement. See MPEP §2422.03.

However to assist the USPTO, it is noted that claim 68 was specifically written along lines of claim 24 without the text in question.

Reconsideration and withdrawal of the sequence listing requirement are requested.

Claims 1, 2, 6-12, 19, 20, 24-26, 29-32, 52-61, 63-67, and 70 stand rejected under §112, first paragraph, as not being enabled. Although Applicant respectfully disagrees, basis for the rejections have been addressed by this submission as follows.

In particular, claims 66-67 are now canceled. The replacement claim suggested by the Examiner at pg. 5 of the Action has been added as new claim 73.

At pgs. 5-6 of the Action, bridging paragraph, the position was taken that recital of "pharmacologically active peptide conjugate" in each of the independent claims is improper. Although Applicant must respectfully disagree with that position, the claims have been amended

in line with the Examiner's request. Specifically, the phrase "pharmacologically active" has been removed from the preamble of the independent claims.

At pg. 6 of the Action, the Examiner has indicated that three claims would be acceptable. The claims have been added as new claims 74, 75 and 76, respectively.

In view thereof, withdrawal of the §112, first paragraph, rejection is respectfully requested.

Claims 1, 2, 6-12, 19, 20, 24-26, 29-32, 52-61, 63-67, and 70 stand rejected under 112, first paragraph, as not being described in the specification. Specifically, the position has been taken that there is no support for "heteropolymeric" and "Z comprises at least two identical amino acid units". Applicant must respectfully disagree with both grounds of rejection.

As an initial matter, it is noted that the test for determining if Applicant's specification complies with the written description requirement is that it reasonably conveys to one of skill in the field that he had possession of the claimed subject matter as of the priority date. There is no obligation that the inventor must satisfy the written description requirement by literally describing the claimed subject matter (*in haec verba*). See MPEP §2163.02. Instead, the test is that Applicant's specification must reasonably convey the inventive concept embodied in the claims to the worker reading his case.

It is respectfully submitted that the claims are in full compliance with the written description requirement.

For example, particular support for "heteropolymeric" in claims 1, 52, 54, 57, 62, 64, and 68 can be found on pg. 9, line 15 to pg. 11, line 27 (disclosing a variety of peptide polymers having more than one amino acid type ie., heteropolymeric peptide sequences). Specific examples of heteropolymeric sequences include enkephalin, Leu-enkephalin, vasopressin, and endolthelin. See also claim 24 as filed originally.

Moreover, a worker reading the instant specification would readily understand that the Applicant was in possession of a variety of conjugates that included heteropolymeric peptide sequences. In support, Applicant submits herewith a peer-reviewed research article that was published well before the priority date of the instant case. As understood, it generally refers to a wide spectrum of protein sequences as "heteropolymer molecules". Dill, K.A (1985) *Biochemistry* 12: 1501. Accordingly, a worker would understand that the present specification reasonably conveyed that the inventor had full possession of the claimed subject matter as of the priority date. Heteropolymeric peptide sequences are amply supported and described by the present application

Specific support for Z being "at least two identical amino acid units" can be found throughout the instant disclosure including pg. 18, lines 26-30 (disclosing "Z" with at least two Lys residues). Further support can be found at pgs. 15-16, bridging paragraph and pg. 16, lines 21-32. See also pg. 19, line 16 to pg. 21, line 9 (disclosing peptide conjugates with particular Z peptides having at least two identical amino acid residues).

Further, claim 1 as filed originally specifically shows the structure of a peptide conjugate that includes "at least two identical amino acid units".

Thus, a worker in this particular field would certainly understand that the specification reasonably conveyed that the inventor had clear possession and had described conjugates in which the Z peptide had "at least two identical amino acid units" as of the priority date.

In view thereof, reconsideration and withdrawal of the §112, first paragraph rejection are requested.

Claims 1, 2, 6-12, 19, 20, 24-26, 29-32, 52-61, 63-67 and 70 stand rejected under §112, second paragraph as being indefinite. The rejection is respectfully traversed in part.

Although Applicant respectfully disagrees with the position taken, the claims have been amended to remove reference to "pharmaceutically active" peptide conjugates as requested

Applicant respectfully disagrees that the claims must be further amended to point out a conjugate having the structure "X-Z". A worker in the field would readily understand from the disclosure and nomenclature accepted in the field as of the priority date that claim 1, for instance, embodies a peptide conjugate in which X and Z are joined via a conventional peptide bond. Peptide bonds and their structure a well known. Accordingly, reference to the bonding of X and Z as used in the claims would not be ambiguous to one who works in this particular field.

Claim 1 was rejected for reciting "at least about 2". Although Applicant disagrees with the rejection, the claim amendments suggested by the Examiner have been adopted.

The claims were rejected for reciting "having a reduced tendency toward enzymatic cleavage". The language has been deleted from the claims.

Claim 19 has been amended as suggested by the Examiner.

In view thereof, reconsideration and withdrawal of the outstanding §112, second paragraph, rejection are earnestly requested.

Claims 1,2, 6-12, 19, 20, 24-26, 29-32, 52-61, 63-65, and 70 stand rejected under §103 as obvious over Docherty or Burger. Applicants respectfully disagrees. The Office has not formulated a *prima facie* case.

As understood, the USPTO has taken the position that the compounds shown on pg. 10 of the Office Action are "obvious over the corresponding homopolymeric peptides". Applicant cannot agree.

As cited, both Docherty and Burger report substantial variation in the activity of Arg, His, and Lys homopolymers, at least in their hands. Within each type of homopolymer, the references disclose further activity variation. Given the "dual" activity variation reported between different homopolymers and within the same type of homopolymer, there is no basis for asserting that the compounds cited at pg. 10 of the Office Action would be "equivalent *a priori*" to any homopolymer including polylysine.

For instance, the cited Docherty paper reports significant variation in the activity of several His, Arg and Lys homopolymers. Variation was supposedly influenced by numerous factors such as the number of amino acids in the homopolymer, pH, target anchoring, hydrophobicity, and secondary structure. See Figures 2, 3 and pg. 1564, cols. 1-2 of Docherty. Burger, as relied on, reports that the activity of a polylysine homopolymer is markedly impacted by concentration, chain length and ionic charge positioning of lysine residues with respect to target. See Burger at pg. 19 and 20-21. The cited references thus report that the activity of His, Arg, and Lys homopolymers varies substantially and that for each homopolymer type there is considerable activity variation depending on a host of different factors.

In the face of this uncertainty, it is not seen how the cited references render the claimed invention obvious. There is no teaching or suggestion in Docherty or Burger that would motivate a worker to modify a polylysine homopolymer to make the compounds shown at pg. 10 of the Office Action. More specifically, the references do not teach or suggest that changing any particular lysine residue to ornithine (Orn) or aminopentylglycine (APG) would be "equivalent a priori" to polylysine. There would be no motivation to make these changes. Quite the contrary, one working in this field would be dissuaded from making those modifications in view of the many different factors reported to impact polylysine activity. There is nothing cited in the references, when taken individually or together, that sheds any light about what amino acid residues could be changed in polylysine, if any, and what that effect would be without risking biological activity cited in the references. See the discussion above.

.In view thereof, there is no grounds for the obviousness rejection and it should be withdrawn.

Claims 1,2, 6-12, 19, 20, 24-26, 29-32, 52-61, 63-65, and 70 stand rejected over Sumner-Smith (US Pat. No. 5,646,120). Applicant respectfully traverses.

As cited, the patent teaches poly-arginine to inhibit HIV replication. However, the claimed invention is not a homopolymer. As such, there is no basis for maintaining the rejection.

In view thereof, it is submitted that bases for the outstanding §103 rejections have been addressed.

Applicant respectfully requests that the USPTO acknowledge priority under §119 to Danish Patent Application No. 0317/98 as filed on March 8, 1998. A certified copy of the document was submitted to the Office on May 11, 2001. If the Examiner requires another certified copy, the undersigned will furnish it on request.

Attached to this submission is a marked-up version of the changes made to the specification and/or claims. The attached page is captioned "version with markings to show changes made".

It is believed that the application is in condition for allowance, which action is earnestly solicited. Although it is not believed that any fee is needed to consider this submission, the USPTO is authorized to charge our deposit account no. **04-1105** should such fee be deemed necessary.

Respectfully submitted,

Date: 8 November 02

By: _____

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PATENT TRADEMARK OFFICE

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claims 66 and 67 have been canceled without prejudice.

Claims 1, 19, 26, 32, 52, 54, 57, 64 and 68 have been amended as follows.

1. (Amended) A [pharmacologically active] peptide conjugate [having a reduced tendency towards enzymatic cleavage] comprising X and Z,

wherein X is a pharmacologically active heteropolymeric peptide sequence, and

wherein Z is a stabilising peptide sequence, of 4-20 amino acid units covalently bonded by its N terminus to the C terminus end of X wherein each amino acid unit in said stabilising peptide sequence, Z is selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Met, Orn, and amino acid units of the general formula I

$$-NH-C(R^1)(R^2)-C(=O)- \qquad (I)$$

wherein R^1 and R^2 are selected from the group consisting of hydrogen, C_{1-6}-alkyl, phenyl, and phenyl-methyl, wherein C_{1-6}-alkyl is optionally substituted with from one to three substituents selected from halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, and phenyl and phenyl-methyl is optionally substituted with from one to three substituents selected from C_{1-6}-alkyl, C_{2-6}-alkenyl, halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, or R^1 and R^2 together with the carbon atom to which they are bound form a cyclopentyl, cyclohexyl, or cycloheptyl ring; and

wherein the ratio between the half-life of said peptide conjugate and the half-life of the corresponding pharmacologically active peptide sequence, X, when treated with carboxypeptidase A or leucine aminopeptidase in about 50 mM phosphate buffer solution at about pH 7.4 at about 37°C or in serum or plasma is at least [about] 2; or a salt thereof, wherein Z comprises at least two identical amino acid units.

19. (Amended) A peptide conjugate according to claim 1, wherein Z is Lys-Lys-Lys-Lys (SEQ ID NO. 55), Xaa-Lys-Lys-Lys, Lys-Xaa-Lys-Lys, Lys-Lys-Xaa-Lys, Lys-Lys-Lys-Xaa, Xaa-Xaa-Lys-Lys, Xaa-Lys-Xaa-Lys, Xaa-Lys-Lys-Xaa, Lys-Xaa-Xaa-Lys, Lys-Xaa-Lys-Xaa, Lys-Lys-Xaa-Xaa, Xaa-Xaa-Xaa-Lys, Xaa-Xaa-Lys-Xaa, Xaa-Lys-Xaa-Xaa, Lys-Xaa-Xaa-Xaa, Xaa-Xaa-Xaa-Xaa, Lys-Lys-Lys-Lys-Lys (SEQ ID NO. 56), Xaa-Lys-Lys-Lys-Lys (SEQ ID NO. 57), Lys-Xaa-Lys-Lys-Lys (SEQ ID NO. 58), Lys-Lys-Xaa-Lys-Lys (SEQ ID NO. 59), Lys-Lys-Lys-Xaa-Lys (SEQ ID NO. 60), Lys-Lys-Lys-Lys-Xaa (SEQ ID NO. 61), Xaa-Xaa-Lys-Lys-Lys, Xaa-Lys-Xaa-Lys-Lys, Xaa-Lys-Lys-Xaa-Lys, Xaa-Lys-Lys-Lys-Xaa, Lys-Xaa-Xaa-Lys-Lys, Lys-Xaa-Lys-Xaa-Lys, Lys-Xaa-Lys-Lys-Xaa, Lys-Lys-Xaa-Xaa-Lys, Lys-Lys-Xaa-Lys-Xaa, Lys-Lys-Lys-Xaa-Xaa, Lys-Lys-Xaa-Xaa-Xaa, Lys-Xaa-Lys-Xaa-Xaa, Lys-Xaa-Xaa-Lys-Xaa, Lys-Xaa-Xaa-Xaa-Lys, Xaa-Lys-Lys-Xaa-Xaa, Xaa-Lys-Xaa-Xaa-Lys, Xaa-Xaa-Lys-Lys-Xaa, Xaa-Xaa-Lys-Xaa-Lys, Xaa-Xaa-Xaa-Lys-Lys, Lys-Xaa-Xaa-Xaa-Xaa, Xaa-Lys-Xaa-Xaa-Xaa, Xaa-Xaa-Lys-Xaa-Xaa, Xaa-Xaa-Xaa-Lys-Xaa, Xaa-Xaa-Xaa-Xaa-Lys, Xaa-Xaa-Xaa-Xaa-Xaa, Lys-Lys-Lys-Lys-Lys-Lys (SEQ ID NO. 62), Xaa-Lys-Lys-Lys-Lys-Lys (SEQ ID NO. 63), Lys-Xaa-Lys-Lys-Lys-Lys (SEQ ID NO. 64), Lys-Lys-Xaa-Lys-Lys-Lys (SEQ ID NO. 65), Lys-Lys-Lys-Xaa-Lys-Lys (SEQ ID NO. 66), Lys-Lys-Lys-Lys-Xaa-Lys (SEQ ID NO. 67), Lys-Lys-Lys-Lys-Lys-Xaa (SEQ ID NO. 68), Xaa-Xaa-Lys-Lys-Lys-Lys (SEQ ID NO. 69), Xaa-

Lys-Xaa-Lys-Lys-Lys (SEQ ID NO. 70), Xaa-Lys-Lys-Xaa-Lys-Lys (SEQ ID NO. 71), Xaa-Lys-Lys-Lys-Xaa-Lys (SEQ ID NO. 72), Xaa-Lys-Lys-Lys-Lys-Xaa (SEQ ID NO. 73), Lys-Xaa-Xaa-Lys-Lys-Lys (SEQ ID NO. 74), Lys-Xaa-Lys-Xaa-Lys-Lys (SEQ ID NO. 75), Lys-Xaa-Lys-Lys-Xaa-Lys (SEQ ID NO. 76), Lys-Xaa-Lys-Lys-Lys-Xaa (SEQ ID NO. 77), Lys-Lys-Xaa-Xaa-Lys-Lys (SEQ ID NO. 78), Lys-Lys-Xaa-Lys-Xaa-Lys (SEQ ID NO. 79), Lys-Lys-Xaa-Lys-Lys-Xaa (SEQ ID NO. 80), Lys-Lys-Lys-Xaa-Xaa-Lys (SEQ ID NO. 81), Lys-Lys-Lys-Xaa-Lys-Xaa (SEQ ID NO. 82), Lys-Lys-Lys-Lys-Xaa-Xaa (SEQ ID NO. 83), Xaa-Xaa-Xaa-Lys-Lys-Lys, Xaa-Xaa-Lys-Xaa-Lys-Lys, Xaa-Xaa-Lys-Lys-Xaa-Lys, Xaa-Xaa-Lys-Lys-Lys-Xaa, Xaa-Lys-Xaa-Xaa-Lys-Lys, Xaa-Lys-Xaa-Lys-Xaa-Lys, Xaa-Lys-Xaa-Lys-Lys-Xaa, Xaa-Lys-Lys-Xaa-Xaa-Lys, Xaa-Lys-Lys-Xaa-Lys-Xaa, Xaa-Lys-Lys-Lys-Xaa-Xaa, Lys-Lys-Lys-Xaa-Xaa-Xaa, Lys-Lys-Xaa-Lys-Xaa-Xaa, Lys-Lys-Xaa-Xaa-Lys-Xaa, Lys-Lys-Xaa-Xaa-Xaa-Lys, Lys-Xaa-Lys-Lys-Xaa-Xaa, Lys-Xaa-Lys-Xaa-Lys-Xaa, Lys-Xaa-Lys-Xaa-Xaa-Lys, Lys-Xaa-Xaa-Lys-Lys-Xaa, Lys-Xaa-Xaa-Lys-Xaa-Lys, Lys-Xaa-Xaa-Xaa-Lys-Lys, Lys-Lys-Xaa-Xaa-Xaa-Xaa, Lys-Xaa-Lys-Xaa-Xaa-Xaa, Lys-Xaa-Xaa-Lys-Xaa-Xaa, Lys-Xaa-Xaa-Xaa-Lys-Xaa, Lys-Xaa-Xaa-Xaa-Xaa-Lys, Xaa-Lys-Lys-Xaa-Xaa-Xaa, Xaa-Lys-Xaa-Lys-Xaa-Xaa, Xaa-Lys-Xaa-Xaa-Lys-Xaa, Xaa-Lys-Xaa-Xaa-Xaa-Lys, Xaa-Xaa-Lys-Lys-Xaa-Xaa, Xaa-Xaa-Lys-Xaa-Lys-Xaa, Xaa-Xaa-Lys-Xaa-Xaa-Lys, Xaa-Xaa-Xaa-Lys-Lys-Xaa, Xaa-Xaa-Xaa-Lys-Lys-Lys, Xaa-Xaa-Xaa-Lys-Xaa-Lys, Xaa-Xaa-Xaa-Xaa-Lys-Lys, Lys-Xaa-Xaa-Xaa-Xaa-Xaa, Xaa-Lys-Xaa-Xaa-Xaa-Xaa, Xaa-Xaa-Lys-Xaa-Xaa-Xaa, Xaa-Xaa-Xaa-Lys-Xaa-Xaa, Xaa-Xaa-Xaa-Xaa-Lys-Xaa, Xaa-Xaa-Xaa-Xaa-Xaa-Lys, or Xaa-Xaa-Xaa-Xaa-Xaa-Xaa, wherein each Xaa is independently selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Arg, His, Met, Orn, and amino acids of the formula I

$-NH-C(R^1)(R^2)-C(=O)-$ (I)

wherein R^1 and R^2 are selected from the group consisting of hydrogen, C_{1-6}-alkyl, phenyl, and phenyl-methyl, wherein C_{1-6}-alkyl is optionally substituted with from one to three substituents selected from halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, and phenyl and phenyl-methyl is optionally substituted with from one to three substituents selected from C_{1-6}-alkyl, C_{2-6}-alkenyl, halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, or R^1 and R^2 together with the carbon atom to which they are [bound] bonded form a cyclopentyl, cyclohexyl, or cycloheptyl ring[, e.g. 2,4-diaminobutanoic acid (Dbu) and 2,3-diaminopropanoic acid (Dpr)].

26. (Amended) A method for the preparation of a [pharmacologically active] peptide conjugate (X-Z) as defined in claim 2, comprising the steps of:

a) coupling an N-α-protected amino acid or N-α-protected dipeptide in the carboxyl activated form, in the C-terminal activated form to an immobilised peptide sequence H-Z-SSM, thereby forming an immobilised N-α-protected peptide fragment,

b) removing the N-α-protecting group, thereby forming an immobilised peptide fragment having an unprotected N-terminal end,

c) coupling an additional N-α-protected amino acid in the carboxyl activated form, or an additional N-α-protected dipeptide in the C-terminal activated form to the N-terminal end of the immobilised peptide fragment, and repeating the removal/coupling step procedure in step b) and c) until the desired peptide sequence X is obtained, and then

d) cleaving off the peptide conjugate from the solid support material.

32. (Amended) A composition comprising a [pharmacologically active] peptide conjugate according to claim 1, and a pharmaceutical acceptable carrier.

52. (Amended) A [pharmacologically active] peptide conjugate [having a reduced tendency towards enzymatic cleavage] comprising X and Z,

wherein X is a pharmacologically active heteropolymeric peptide sequence, and

wherein Z is a stabilising peptide sequence of 4-20 amino acid units covalently bound by its N terminus to the C terminus end of X, wherein each amino acid unit in said stabilising peptide sequence Z is selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Met, Orn, and amino acid units of the general formula I

$$-NH-C(R^1)(R^2)-C(=O)- \qquad (I)$$

wherein R^1 and R^2 are selected from the group consisting of hydrogen, C_{1-6}-alkyl, phenyl, and phenyl-methyl, wherein C_{1-6}-alkyl is optionally substituted with from one to three substituents selected from halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, and phenyl and phenyl-methyl is optionally substituted with from one to three substituents selected from C_{1-6}-alkyl, C_{2-6}-alkenyl, halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, or R^1 and R^2 together with the carbon atom to which they are bound form a cyclopentyl, cyclohexyl, or cycloheptyl ring; and

wherein the ratio between the half-life of said peptide conjugate and the half-life of the corresponding pharmacologically active peptide sequence X, when treated with carboxypeptidase A or leucine aminopeptidase in about 50 mM phosphate buffer solution at about pH 7.4 at about 37°C or in serum or plasma is at least [about] 3; or a salt thereof, wherein Z comprises at least two identical amino acid units.

54. (Amended) A [pharmacologically active] peptide conjugate [having a reduced tendency towards enzymatic cleavage] comprising X and Z,

wherein X is a pharmacologically active heteropolymeric peptide sequence, and

wherein Z is a stabilising peptide sequence of 4-10 amino acid units covalently bound by its N terminus to the C terminus end of X, wherein each amino acid unit in said stabilising peptide sequence Z is selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Met, Orn, and amino acid units of the general formula I

$$-NH-C(R^1)(R^2)-C(=O)- \qquad (I)$$

wherein R^1 and R^2 are selected from the group consisting of hydrogen, C_{1-6}-alkyl, phenyl, and phenyl-methyl, wherein C_{1-6}-alkyl is optionally substituted with from one to three substituents selected from halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, and phenyl and phenyl-methyl is optionally substituted with from one to three substituents selected from C_{1-6}-alkyl, C_{2-6}-alkenyl, halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, or R^1 and R^2 together with the carbon atom to which they are bound form a cyclopentyl, cyclohexyl, or cycloheptyl ring; and

wherein the ratio between the half-life of said peptide conjugate and the half-life of the corresponding pharmacologically active peptide sequence X, when treated with carboxypeptidase A or leucine aminopeptidase in about 50 mM phosphate buffer solution at about pH 7.4 at about 37°C or in serum or plasma is at least [about] 2; or a salt thereof, wherein Z comprises at least two identical amino acid units.

57. (Amended) A [pharmacologically active] peptide conjugate [having a reduced tendency towards enzymatic cleavage] comprising X and Z,

wherein X is a pharmacologically active heteropolymeric peptide sequence, and

wherein Z is a stabilising peptide sequence of 4-20 amino acid units covalently bound by its N terminus to the C terminus end of X, wherein each amino acid unit in said stabilising peptide sequence Z is selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Met, Orn, and amino acid units of the general formula I

$$-NH-C(R^1)(R^2)-C(=O)- \qquad (I)$$

wherein R^1 and R^2 are selected from the group consisting of hydrogen, C_{1-6}-alkyl, phenyl, and phenyl-methyl, wherein C_{1-6}-alkyl is optionally substituted with from one to three substituents selected from halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, and phenyl and phenyl-methyl is optionally substituted with from one to three substituents selected from C_{1-6}-alkyl, C_{2-6}-alkenyl, halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, or R^1 and R^2 together with the carbon atom to which they are bound form a cyclopentyl, cyclohexyl, or cycloheptyl ring; and

wherein the ratio between the half-life of said peptide conjugate and the half-life of the corresponding pharmacologically active peptide sequence X, when treated with carboxypeptidase A or leucine aminopeptidase in about 50 mM phosphate buffer solution at about pH 7.4 at about 37°C or in serum or plasma is at least [about] 2; or a salt thereof, wherein Z comprises at least two or three Lys amino acid units.

64. (Amended) A [pharmacologically active] peptide conjugate [having a reduced tendency towards enzymatic cleavage] comprising X and Z,

wherein X is a pharmacologically active heteropolymeric peptide sequence, and

wherein Z is a stabilising peptide sequence of 4-20 amino acid units covalently bound by its N terminus to the C terminus end of X, wherein each amino acid unit in said stabilising peptide sequence Z is selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Met, Orn, and amino acid units of the general formula I

$$-NH-C(R^1)(R^2)-C(=O)- \qquad (I)$$

wherein R^1 and R^2 are selected from the group consisting of hydrogen, C_{1-6}-alkyl, phenyl, and phenyl-methyl, wherein C_{1-6}-alkyl is optionally substituted with from one to three substituents selected from halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, and phenyl and phenyl-methyl is optionally substituted with from one to three substituents selected from C_{1-6}-alkyl, C_{2-6}-alkenyl, halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, or R^1 and R^2 together with the carbon atom to which they are bound form a cyclopentyl, cyclohexyl, or cycloheptyl ring; and

wherein the ratio between the half-life of said peptide conjugate and the half-life of the corresponding pharmacologically active peptide sequence X, when treated with carboxypeptidase A or leucine aminopeptidase in about 50 mM phosphate buffer solution at about pH 7.4 at about 37°C or in serum or plasma is at least [about] 2; or a salt thereof, wherein said pharmacologically active peptide sequence (X) consists of at the most about 65 amino acid units, wherein Z comprises at least two identical amino acid units.

68. (Amended) A [pharmacologically active] peptide conjugate [having a reduced tendency towards enzymatic cleavage] comprising X and Z,

wherein X is a pharmacologically active heteropolymeric peptide sequence, and

wherein Z is a stabilising peptide sequence of 4-20 amino acid units covalently bound by its N terminus to the C terminus end of X, wherein each amino acid unit in said stabilising peptide sequence Z is selected from the group consisting of Ala, Leu, Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His, Met, Orn, and amino acid units of the general formula I

$$-NH-C(R^1)(R^2)-C(=O)- \qquad (I)$$

wherein R^1 and R^2 are selected from the group consisting of hydrogen, C_{1-6}-alkyl, phenyl, and phenyl-methyl, wherein C_{1-6}-alkyl is optionally substituted with from one to three substituents selected from halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, and phenyl and phenyl-methyl is optionally substituted with from one to three substituents selected from C_{1-6}-alkyl, C_{2-6}-alkenyl, halogen, hydroxy, amino, cyano, nitro, sulfono, and carboxy, or R^1 and R^2 together with the carbon atom to which they are bound form a cyclopentyl, cyclohexyl, or cycloheptyl ring; and

wherein the ratio between the half-life of said peptide conjugate and the half-life of the corresponding pharmacologically active peptide sequence X, when treated with carboxypeptidase A or leucine aminopeptidase in about 50 mM phosphate buffer solution at about pH 7.4 at about 37°C or in serum or plasma is at least [about] 2; or a salt thereof,

wherein,

Z is Lys_p-Xaa_q or Xaa_p-Lys_q, wherein p and q are integers in the range from 1 to 14, with the proviso that p+q is in the range of 3-15, and each Xaa is independently selected from the group consisting of Ser, Thr, Tyr, Asn, Gln, Asp, Glu, Arg, His, Orn, 2,4-diaminobutanoic acid, 2,3-diaminopropanoic acid and Met,

and further wherein,

X is selected from the group consisting of AF 12505 (Ile-Glu-Gly-Pro-Thr-Leu-Arg-Gln-Trp-Leu-Ala-Ala-Arg-Ala) (SEQ ID NO. 14), insulin-like growth factor I (57-70) (Ala-Leu-Leu-Glu-Thr-Tyr-Cys-Ala-Thr-Pro-Ala-Lys-Ser-Glu) (SEQ ID NO. 15), insulin-like growth factor I (30-41) (Gly-Tyr-Gly-Ser-Ser-Ser-Arg-Arg-Ala-Pro-Gln-Thr) (SEQ ID NO. 16), insulin-like growth factor I (24-41)(Tyr-Phe-Asn-Lys-Pro-Thr-Gly-Tyr-Gly-Ser-Ser-Ser-Arg-Arg-Ala-Pro-Gln-Thr) (SEQ ID NO. 17) , insulin-like growth factor II (33-40) (Ser-Arg-Val-Ser-Arg-Arg-Ser-Arg) (SEQ ID NO. 18), insulin-like growth factor II (33-40) (Tyr-Ser-Arg-Val-Ser-Arg-Arg-Ser-Arg) (SEQ ID NO. 19), insulin-like growth factor II (69-84) (Asp-Val-Ser-Thr-Pro-Pro-Thr-Val-Leu-Pro-Asp-Asn-Phe-Pro- Arg-Tyr) (SEQ ID NO. 20), growth hormone (GH)-releasing peptide-6 (GHRP-6) (His-DTrp-Ala-Trp-DPhe-Lys-NH2) (SEQ ID NO. 21), beta-Interleukin I (163-171) (Val-Gln-Gly-Glu-Glu-Ser-Asn-Asp-Lys) (SEQ ID NO. 22), beta-Interleukin II (44-56) (Ile-Leu-Asn-Gly-Ile-Asn-Asn-Tyr-Lys-Asn-Pro-Lys-Leu) (SEQ ID NO. 23), Interleukin II (60-70) (Leu-Thr-Phe-Lys-Phe-Tyr-Met-Pro-Lys-Lys-Ala) (SEQ ID NO. 24), exendin-4 (GLP-1 analog) (His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-NH2) (SEQ ID NO. 25), exendin-3 (GLP-1 analog) (His-Ser-Asp-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser) (SEQ ID NO. 26), epidermal growth factor (20-

31) Cys(Acm)-Met-His-Ile-Glu-Ser-Leu-Asp-Ser-Tyr-Thr-Cys(Acm) (SEQ ID NO. 27), bivalirudin (Hirulog) (D-Phe-Pro-Arg-Pro-(Gly)4-Asn-Gly-Asp-Phe-Glu-Glu-Ile-Pro-Glu-Glu-Tyr-Leu) (SEQ ID NO. 28), hirulog-1 D-Phe-Pro-Arg-Pro-(Gly)4-Asn-Gly-Asp-Phe-Glu-Glu-Ile-Pro-Glu-Tyr-Leu (SEQ ID NO. 29), C-type natriuretic peptide (1-53) (CNP) (Asp-Leu-Arg-Val-Asp-Thr-Lys-Ser-Arg-Ala-Ala-Trp-Ala-Arg-Leu-Leu-Gln-Glu-His-Pro-Asn-Ala-Arg-Lys-Tyr-Lys-Gly-Ala-Asn-Lys-Lys-Gly-Leu-Ser-Lys-Gly-Cys-Phe-Gly-Leu-Lys-Leu-Asp-Arg-Ile-Gly-Ser-Met-Ser-Gly-Leu-Gly-Cys; Disulfide bridge: Cys37-Cys53) (SEQ ID NO. 30), "Mini ANP" (Met-Cys-His-cyclohexylAla-Gly-Gly-Arg-Met-Asp-Arg-Ile-Ser-Cys-Tyr-Arg, disulfide bridge cys2-cys13) (SEQ ID NO. 31), Melanotan-II (MT-II, alpha-MSH4-10-NH2, or Ac-Nle4-Asp5-His6-D-Phe7-Arg8-Trp9-Lys10) (SEQ ID NO. 32), thymosin alpha1 (TA1) (Ac-Ser-Asp-Ala-Ala-Val-Asp-Thr-Ser-Ser-Glu-Ile-Thr-Thr-Lys-Asp-Leu-Lys-Glu-Lys-Lys-Glu-Val-Val-Glu-Glu-Ala-Glu-Asn) (SEQ ID NO. 33), Cys-Phe-Ile-Gln-Asn-Cys-Pro-Orn-Gly-NH2, Disulfide bridge: Cys1-Cys6) (SEQ ID NO. 34), octreotide (201-995) (DPhe-Cys-Phe-DTrp-Lys-Thr-Cys-Thr-ol; disulfide bridge: Cys2-Cys7) (SEQ ID NO. 35), calcitonin gene-related peptide (CGRP) (Ala-Cys-Asp-Thr-Ala-Thr-Cys-Val-Thr-His-Arg-Leu-Ala-Gly-Leu-Leu-Ser-Arg-Ser-Gly-Gly-Val-Val-Lys-Asn-Asn-Phe-Val-Pro-Thr-Asn-Val-Gly-Ser-Lys-Ala-Phe-NH_2; Disulfide bridge: Cys2-Cys7) (SEQ ID NO. 36), endomorphin-1 Tyr-Pro-Trp-Phe-NH2 (SEQ ID NO. 37); endomorphin-2 Tyr-Pro-Phe-Phe-NH_2 (SEQ ID NO. 38), nociceptin (also known as Orphanin FQ, Phe-Gly-Gly-Phe-Thr-Gly-Ala-Arg-Lys-Ser-Ala-Arg-Lys-Leu-Ala-Asn-Gln) (SEQ ID NO. 39), angiotensinogen (1-13) (Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu-Val-Ile-His) (SEQ ID NO. 40), adrenomodullin (1-12) (Tyr-Arg-Gln-Ser-Met-Asn-Asn-Phe-Gln-Gly-Leu-Arg) (SEQ ID NO. 41), antiarrhytmic peptide (AAP) (Gly-Pro-Hyp-Gly-Ala-Gly) (SEQ ID NO. 42), Antagonist G (Arg-DTrp-(nMe)Phe-DTrp-Leu-Met-NH_2), indolicidin (Ile-Leu-Pro-Trp-Lys-Trp-Pro-Trp-Trp-Pro-Trp-Arg-Arg-NH_2) (SEQ ID NO. 43), osteocalcin (37-49) (Gly-Phe-Gln-Glu-Ala-Tyr-Arg-Arg-Phe-Tyr-Gly-Pro-Val) (SEQ ID NO. 44), cortistatin 29 (1-13) (Glp)-Glu-Arg-Pro-Pro-Leu-Gln-Gln-Pro-Pro-His-Arg-Asp) (SEQ ID NO. 45), cortistatin 14 Pro-Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Ser-Ser-Cys-Lys; Disulfide bridge: Cys2-Cys13 (SEQ ID NO. 46), PD-145065 (Ac-D-Bhg-Leu-Asp-Ile-Ile-Trp) (SEQ ID NO. 47), PD-142893 (Ac-D-Dip-Leu-Asp-Ile-Ile-Trp) (SEQ ID NO. 48), fibrinogen binding inhibitor peptide (His-His-Leu-Gly-Gly-Ala-Lys-Gln-Ala-Gly-Asp-Val) (SEQ ID NO. 49), leptin (93-105) (Asn-Val-

Ile-Gln-Ile-Ser-Asn-Asp-Leu-Glu-Asn-Leu-Arg) (SEQ ID NO. 50), GR 83074 (Boc-Arg-Ala-DTrp-Phe-DPro-Pro-Nle-NH_2) (SEQ ID NO. 51) Tyr-W-MIF-1 (Tyr-Pro-Trp-Gly-NH_2) (SEQ ID NO. 52), parathyroid hormone related peptide (107-111) (Thr-Arg-Ser-Ala-Trp) (SEQ ID NO. 53), angiotensinogen (1-14) Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu-Val-Ile-His-Asn (SEQ ID NO. 54), Leupeptin (Ac-Leu-Leu-Arg-CHO); [or a modified fragment thereof;] and further wherein Z comprises at least two identical amino acid units.

Kindly add the following new claims 73-77.

73. (New) A method of achieving binding between the conjugate of claim 1 and μ opioid receptors comprising administering to the subject in need thereof the conjugate for a time and under conditions effective to achieve binding between said conjugate and μ opioid receptors.

74. (New) A composition comprising a pharmaceutically acceptable carrier and a conjugate according to claim 1 in an amount effective to bind μ opioid receptors.

75. (New) A composition comprising a pharmaceutically acceptable carrier, and a conjugate according to claim 1 in an amount effective to stimulate erythroposiesis.

76. (New) A composition comprising a pharmaceutically acceptable carrier, and a conjuage according to claim 1 in an amount effective to induce retraction of osteoblasts.

77. (New) The peptide conjugate of claim 1, wherein the conjugate is represented by the following sequence: Ac-Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-$(Lys)_6$-NH_2 or a fragment thereof.

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